The Examiner states that "[c]laim 1 is indefinite in reciting 'capable of' because it fails to recite a positive and active method step.

Claim 1 has been amended to replace the phrase "is capable of binding" with the term "binds".

The Examiner also states that claim 1 is incomplete for omitting the label which provides for effecting the generation of a signal upon binding of the first binding partner and the protein."

Claim 1 has been amended to claim a "labeled first binding partner".

The Examiner has also rejected claim 1 for being vague and indefinite in the recitation of "detecting labeling of the protein by the first binding partner because as recited, it appears that the protein has a label conjugated thereto wherein signal generation is effected by the binding of an 'unlabeled' first binding partner to the 'labeled' protein which is not what Applicants intend based on subsequent claims".

Claim 1 has been amended to claim "detecting said protein by the binding of the labelled first binding partner to said protein".

Claim 5 is rejected for being vague in the recitation of the phrase, "the protein is isolated by binding to said capture ligand because it is unclear what is encompassed by the term 'isolated' in relation to the 'capture ligand'."

Claim 5, as amended, claims "said protein that binds to said capture ligand is isolated from said protein that does not bind to said capture ligand".

Claims 4 and 6 are rejected for being inconsistent in the recitation of "solid phase substrate" in claim 4 and "solid phase support" in claim 6.

Applicants have amended claim 6 to replace "support" with "substrate".

Claims 7 and 22 are rejected for being indefinite in the recitation of "and/or".

Applicants have amended claims 7 and 22 to delete the phrase "and/or.

Claim 7 is also rejected for being indefinite in the recitation of the phrase "other".

Applicants have deleted the term "other" from amended claim 7.

Claim 7 is also rejected for reciting an improper and overlapping Markush group.

Amended claim 7 recites a proper Markush group.

Claim 10 is rejected for reciting the abbreviation "FRET" and claim 14 is rejected for reciting the abbreviation "FCS". Claims 10 and 14 have been amended to recite "fluorescence resonance energy transfer (FRET)" and "fluorescence correlation spectroscopy (FCS)", respectively.

The Examiner states that claim 13 is vague and indefinite in reciting "unbound labelled binding partner because it is unclear as to which "binding partner" is being referred to.

Claim 13 has been amended to claim "unbound labelled first binding partner" and "labelled first binding partner".

In view of all of the above, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, second paragraph rejection of claims 1-14 and 20-22.

Provisional Double Patenting Rejection of Claims 1, 3-14 and 19-22 under 35 U.S.C. § 101

Claims 1, 3-14 and 19-22 are provisionally rejected under 35 U.S.C. § 101 for allegedly claiming the same invention as that of claims 1-13 and 18-21 of copending Application 09/258,452.

Applicants submit that claim 1 and dependent claims 4-8 and 9-14 have been amended to include the limitation "a) contacting a protein with a labeled first binding partner which binds to said protein in a manner dependent on the conformational state of said protein, and which generates a signal in a manner dependent on the binding of the first binding partner to the protein, and a labeled second binding partner which binds to said protein, wherein said protein and said labeled binding partner are not covalently coupled". Applicants submit that claims 1-13 of copending Application 09/258,452 do not include this limitation and are therefore distinct from claims 1, 4-8 and 10-14 of the instant application.

Claims 3 and 9 have been cancelled.

Claim 19 has been amended to include the limitation of a "a labelled first binding partner which binds to the protein in a manner dependent on the conformational state of the protein and is detectable in a manner dependent on its binding to the protein, and a labelled second binding partner, wherein said protein and said first binding partner are not covalently coupled".

Applicants submit that claims 18-21 of copending Application 09/258,452 do not include this limitation and are therefore distinct from claim 19 of the instant application.

Claim 20 and dependent claims 21-22 have been amended to include the limitation, "a labelled first binding partner which binds to the protein in a manner dependent on the conformational state of the protein and is detectable in a manner dependent on its binding to the protein and a labelled second binding partner, wherein said protein and said first binding partner or said second binding partner are not covalently coupled".

Applicants submit that claims 18-21 of copending Application 09/258,452 do not include this limitation and are therefore distinct from claim 20-22 of the instant application.

In view of the above, Applicants respectfully request withdrawal of the provisional double patenting rejection of claims 1, 3-14 and 19-22.

Rejection of Claims 1, 3-9 and 12-13 under 35 U.S.C. § 102(e)

Claims 1, 3-9 and 12-13 are rejected under 35 U.S.C. § 102(e) for allegedly being anticipated by Prusiner et al. (U.S. 5,891,641).

The Examiner states that "Prusiner et al. disclose a method for determining a diseased related conformational state of a protein such as PrP^{SC} in a sample...contacting the protein with a labeled antibody that binds (has a higher binding affinity) to the protein in a manner dependent on the conformational state of the protein...Prusiner et al. also disclose contacting the protein with a second antibody or capture ligand to immobilize the protein on a solid phase substrate (see column 4, lines 5-10)."

Amended claim 1 and dependent claims 4-8 and 12-13 claim "a method for determining the conformational state of a protein, comprising the steps of: a) contacting a protein with a labeled first binding partner which binds to said protein in a manner dependent on the conformational state of said protein and which generates a signal in a manner dependent on the binding of the first binding partner to the protein, and a labeled second binding partner which binds to said protein, wherein said protein and said labeled first or second binding partner are not covalently coupled; and b) detecting said protein by the binding of at least one of said labeled first binding partner or said labelled second binding partner to said protein wherein labelling of said protein is an indicator of the conformational state of said protein."

Claims 3 and 9 have been cancelled.

Applicants submit that Prusiner et al. teach an assay for determining the presence of a disease related conformation of a protein that comprises the following steps:

> "[t]he assay is carried out by providing a sample which is divided into a first portion and a second portion. The first portion is bound to a first solid support and then contacted with a labeled antibody which binds to the non-disease form of the protein with a higher degree of affinity...than the antibody binds to the disease form. The second portion of the sample is treated in a manner which causes the tightly bound disease form of the protein present in the sample (if any) to assume a more relaxed conformation which has a higher binding affinity to the labeled antibody. After treatment the second portion is

also bound to the surface of a solid support. Thereafter, the second portion is contacted with the same type of labeled antibodies which were used on the first portion." (column 3, line 65- column 4, line 12)

Thus, Prusiner et al. do not teach "contacting a protein with a labeled first binding partner which binds to said protein in a manner dependent on the conformational state of said protein and which generates a signal in a manner dependent on the binding of the first binding partner to the protein, and a labeled second binding partner which binds to said protein, wherein said protein and said labeled first or second binding partner are not covalently coupled" as claimed in claim 1. Rather, Prusiner et al. teach contacting a protein in a first conformation with a labeled antibody and contacting a separate aliquot of the same protein in a second conformation with the same labeled antibody.

Prusiner et al. do not teach all of the elements of claim 1 and therefore do not anticipate claims 1, 3-9 and 12-13 of the instant application.

In view of the above, Applicants respectfully request withdrawal of the rejection of claims 1, 3-9 and 12-13 under 35 U.S.C. § 102(e) in view of Prusiner et al. (U.S. 5,891,641).

Rejection of Claims 1, 3-9 and 12-13 under 35 U.S.C. § 102(e)

Claims 1, 3-9 and 12-13 are rejected under 35 U.S.C. § 102(e) for allegedly being anticipated by Martinez et al. (WO 98/41872).

The Examiner states that "Martinez et al. disclose a method for determining a conformational state of a protein (activated versus inactivated) such as a cytokine receptor or growth hormone receptor (GHR) in a sample. Martinez et al. specifically disclose contacting the protein with an antibody (GHR05) that selectively binds to the protein in a manner dependent on its conformational state, thereby forming a complex... Martinez et al. disclose contacting the protein with a second antibody or capture ligand to immobilize the protein on a solid phase substrate in a sandwich capture assay (see page 7, lines 26-30). Alternatively, the protein can be covalently linked to avidin-coated solid phase substrate (microtiter plate) to capture the antibody in an antibody capture assay (see page 7, lines 10-19)."

Amended claim 1 and dependent claims 4-8 and 12-13 claim "a method for determining the conformational state of a protein, comprising the steps of: a) contacting a protein with a labeled first binding partner which binds to said protein in a manner dependent on the conformational state of said protein and which generates a signal in a manner dependent on the binding of the first binding partner to the protein, and a labeled second binding partner which

binds to said protein, wherein said protein and said labeled first or second binding partner are not covalently coupled; and b) detecting said protein by the binding of at least one of said labeled first binding partner or said labelled second binding partner to said protein wherein labelling of said protein is an indicator of the conformational state of said protein."

Claims 3 and 9 have been cancelled.

Applicants submit that Martinez et al. teach a method for determining cytokine receptor activation that uses an antibody that discriminates between an activated and an inactivated cytokine receptor conformation or cytokine receptor binding protein conformation. Martinez et al. teach an antibody capture assay at p. 7, lines 10-18 wherein biotin-labeled growth hormone binding protein (GHBP) is bound to avidin-coated microtiter plates, and incubated with mouse-anti-GHBP antibody followed by goat anti-mouse antibody. Martinez et al. also teaches a sandwich capture assay wherein anti-GHBP mAb is bound to microtiter plates and then incubated, sequentially, with 1. GHBP, 2. biotin-labeled, anti-GHBP second mAb and 3. PO-streptavidin and OPD.

Thus, Martinez et al. do not teach "contacting a protein with a labeled first binding partner which binds to said protein in a manner dependent on the conformational state of said protein and which generates a signal in a manner dependent on the binding of the first binding partner to the protein, and a labeled second binding partner which binds to said protein, wherein said protein and said labeled first or second binding partner are not covalently coupled" as claimed in claim 1. Rather, Martinez et al. teach contacting a protein with a labeled first antibody and a second unlabeled antibody.

Martinez et al. do not teach all of the elements of claim 1 and therefore do not anticipate claims 1, 3-9 and 12-13 of the instant application.

In view of the above, Applicants respectfully request withdrawal of the rejection of claims 1, 3-9 and 12-13 under 35 U.S.C. § 102(e) in view of Martinez et al. (WO 98/41872).

Rejection of Claims 1, 3 and 7-11 under 35 U.S.C. § 102(e)

Claims 1, 3 and 7-11 are rejected under 35 U.S.C. § 102(e) for allegedly being anticipated by Tsien et al. (U.S. 5,998,204).

The Office Action states that Tsien et al. discloses "fluorescent indicators and methods for using them to determine concentration of binding partners (analyte) by determining a change in the conformational state of a binding protein...Tsien et al. disclose the fluorescence indicators comprising a protein (binding protein) that changes conformation upon binding a first binding

partner, wherein a first label (donor fluorescent moiety) is covalently bound to a binding protein moiety and a second label (acceptor fluorescent moiety) is covalently bound to a binding protein moiety so that when the binding protein binds a binding partner, the fluorescent indicator is caused to change in conformation. "

Claim 1 and dependent claims 7, 8, 10 and 11 claim "a method for determining the conformational state of a protein, comprising the steps of: a) contacting a protein with a labeled first binding partner which binds to said protein in a manner dependent on the conformational state of said protein and which generates a signal in a manner dependent on the binding of the first binding partner to the protein, and a labeled second binding partner which binds to said protein, **wherein said protein and said labeled first or second binding partner are not covalently coupled**; and b) detecting said protein by the binding of at least one of said labeled first binding partner or said labelled second binding partner to said protein wherein labelling of said protein is an indicator of the conformational state of said protein."

Claims 3 and 9 are cancelled.

As pointed out by the Office Action, Tsien et al. specifically requires that the donor fluorescent protein moiety and the acceptor fluorescent protein moiety be covalently coupled to the binding protein moiety. According to the invention of Tsien et al., the donor fluorescent protein moiety and the acceptor fluorescent protein moiety are required to be covalently coupled, and a rigid attachment of these protein moieties to the binding protein moiety is necessary for the sensitive detection of ligand-induced conformational changes. It is stated in Tsien et al., at column 5, paragraph 3:

> "If the GFP donor and acceptor are fused to a host protein rigidly, minor changes in the relative orientation of the ends of the latter would alter FRET. In contrast, most conventional fluorescent labels are attached by flexible linkers that at least partially decouple the fluorophore orientation from that of the protein to which its is attached, limiting the sensitivity of the FRET measurement".

Claims 1, 3 and 7-11 of the instant application require that the protein and the labelled first or second binding partner are not covalently coupled. The specification of the present invention clearly teaches that the binding partner and the protein of the present invention are not required to be covalently coupled to the protein whose conformation change is to be detected. Furthermore, Applicants submit that the method of the claimed invention would not work if the

protein and binding partner were covalently coupled. The recited methods for detecting "said protein by the binding of at least one of said labelled first binding partner or said labelled second binding partner to said protein", that is the method of detecting association of the protein by the binding of the first binding partner and/or the second binding partner, would not work with a covalently coupled protein and binding partner.

For example, on page 6, lines 31-p. 7, line 3, the present invention states:

> "In a second configuration, the association of the protein and the binding partner may be measured by mass, such as by surface plasmon resonance. In this example, binding of the binding partner to the protein causes a change in the mass thereof; unbound binding partner causes no change in mass, and is therefore not detectable".

It is clear that the binding partner in the above example is not covalently linked to the protein. Otherwise, the binding of the binding partner to the protein would not result in a change in mass which could be detected by surface plasmon resonance.

The present invention also states:

> "Additional embodiments of the present invention are not dependent on FRET. For example the invention can make use of fluorescence correlation spectroscopy (FCS), which relies on the measurement of the rate of diffusion of a label...A labelled molecule will diffuse at a slower rate if it is larger than if it is small. Thus, binding partners bound to proteins will display slow diffusion rates, resulting in a lower number of fluorescent bursts in any given timeframe, whilst labelled binding partners which are not bound to proteins will diffuse more rapidly" (page 21, line 31- page 32, line 1 and page 32, lines 13-16).
> "A further detection technique which may be employed in the method of the present invention is the measurement of time-dependent decay of the fluorescence anisotropy...Fluorescence anisotropy relies on the measurement of the rotation of fluorescent groups. Larger proteins rotate more slowly than smaller binding partners, allowing the formation of protein:binding partner associations to be monitored" (page 31 paragraphs 4-5).

It is clear from reading the above examples that the detection methods of the present invention would not be successful with a binding partner(s) covalently linked to a protein. Neither FCS nor fluorescence anisotropy would be applicable to the present invention because

both techniques depend on a change of movement of the labeled binding partner(s) due to an increased mass caused by binding of the binding partner(s) to the protein.

As seen in the above examples, the present invention teaches two techniques in addition to FRET for the detection of conformational changes of the protein. One technique is fluorescence correlation spectroscopy (FCS), which relies on the measurement of the rate of diffusion of a label (page 22, lines 7-11). The other is fluorescence anisotropy which measures a time-dependent fluorescence decay (page 22, lines 28-30). Tsien et al. does not teach the use of FCS or fluorescence antisotropy.

The attached Rule 1.132 declaration of Dr. Woolfson teaches the advantages of using a non-covalently attached protein-binding partner pair, as compared to covalently associated fluorescent indicator molecules of Tsien et al. These advantages are as follows:

The claimed methods can be performed with a variety of detection methods that are dependent on detecting a change in mass that occurs as a result of binding. The claimed methods can be carried out using a variety of fluorescent labels. By using non-covalently associated protein binding partner(s), the claimed methods can be carried out with a protein and a binding partner that have been labeled in separate reactions. A variety of proteins and binding partners, (wherein variety refers to each protein or binding moiety comprising a different label) can be prepared easily from a single pool of purified protein and binding partner(s). The claimed methods can be carried out using a single fluorescent label or more than one label. The claimed methods can be optimized by varying the ratio of protein and binding partner, but do not require optimization of linker length since these methods do not use a linker.

In view of the above, Applicants submit that the present invention is not anticipated by Tsien et al.

Applicants respectfully request the withdrawal of the 35 U.S.C. § 102(e) rejections of claims 1, 3 and 7-11 in view of Tsien et al.

Rejection of Claims 2-3, 5-9 and 11 under 35 U.S.C. § 102(e)

Claims 2-3, 5-9 and 11 are rejected under 35 U.S.C. § 102(e) for allegedly being anticipated by Eberwine et al. (WO 96/05847).

The Examiner states that "Eberwine et al. disclose measuring activity of an enzyme wherein the conformation of a protein is dependent upon the post-translational modification activity of the enzyme. Eberwine et al. disclose contacting the protein which has a site (epitope) for post-translational modification with the enzyme. Eberwine et al. further disclose adding

antibodies to bind at least two epitopes on the protein wherein one of the antibodies binds the protein in a manner dependent upon or specific for the post-translational modification of the enzyme. For detection, the antibodies are first modified by binding thereto, a first and a second nucleotide sequence."

Amended claim 2 and dependent claims 5-9 and 11 claim "a method for measuring the activity of an enzyme, wherein the conformation of a protein is dependent upon the post-translational modification activity of the enzyme, the method comprising the steps of: a) contacting a protein comprising a site for post-translational modification with the enzyme; b) providing a labelled first binding partner which binds to the protein in a manner dependent on the post-translational modification of the protein by the enzyme and which generates a signal in a manner dependent on said post-translational modification, and a second labelled binding partner which binds to said protein; c) contacting the protein with the labelled first binding partner and the labelled second binding partner and determining the post-translational modifying activity of the enzyme."

Claims 3 and 9 have been cancelled.

Applicants submit that Eberwine et al. teach a method for identifying an amino acid sequence of a protein and characterizing post-translational events occurring on the protein by epitope ordering followed by restriction mapping. The method of Eberwine et al. does not use labeled antibodies but rather uses antibodies bound to nucleotide sequences.

Thus, Eberwine et al. do not teach "providing a labelled first binding partner which binds to the protein in a manner dependent on the post-translational modification of the protein by the enzyme and which generates a signal in a manner dependent on said post-translational modification, and a second labelled binding partner which binds to said protein", as claimed in amended claim 2. Rather, Eberwine et al. teach contacting a protein with a first unlabeled antibody bound to a nucleotide sequence and a second unlabeled antibody bound to a nucleotide sequence.

Eberwine et al. do not teach all of the elements of claim 2 and therefore do not anticipate claims 2-3, 5-9 and 11 of the instant application.

In view of the above, Applicants respectfully request withdrawal of the rejection of claims 2-3, 5-9 and 11 under 35 U.S.C. § 102(e) in view of Eberwine et al. (WO 96/05847).

Rejection of Claims 2-14 under 35 U.S.C. § 102(e)

Claims 2-14 are rejected under 35 U.S.C. § 102(e) for allegedly being anticipated by Epps et al. (U.S. 6,203,994).

The Examiner states that "Epps et al. disclose measuring activity of an enzyme wherein the conformation of a protein is dependent upon the post-translational modification activity of the enzyme...Epps et al. disclose contacting the enzyme with a protein (amino acid) that is capable of being phosphorylated by the enzyme and a reporter molecule comprising a fluorescent label and a phosphorylated protein, and an antibody that selectively binds to the phosphorylated protein...Epps et al. disclose that the antibody binds the protein in a manner dependent upon the post –translational modification by the enzyme."

Amended claim 2 and dependent claims 4-8 and 10-14 claim "a method for measuring the activity of an enzyme, wherein the conformation of a protein is dependent upon the post-translational modification activity of the enzyme, the method comprising the steps of: a) contacting a protein comprising a site for post-translational modification with the enzyme; b) providing a labelled first binding partner which binds to the protein in a manner dependent on the post-translational modification of the protein by the enzyme and which generates a signal in a manner dependent on said post-translational modification, and a second labelled binding partner which binds to said protein; c) contacting the protein with the labelled first binding partner and the labelled second binding partner and determining the post-translational modifying activity of the enzyme."

Claims 3 and 9 have been cancelled.

Applicants submit that Epps et al. teach fluorescence based assays for determining the amount of a substrate that is phosphorylated or dephosphorylated during a kinase or phosphatase reaction and/or the activity of a kinase or phosphatase.

It is stated in Epps at column 4, lines 20-40,

> "[t]hus, in another embodiment, the invention relates to a method of determining the phosphorylating activity of an enzyme comprising the steps of: (a) combining the enzyme with: (i) a substrate molecule comprising an amino acid selected from the group consisting of Ser, Thr, and Tyr, wherein said substrate molecule is capable of being phosphorylated at said amino acid by said enzyme to yield a product, and wherein said substrate molecule is labeled with an acceptor fluorophore; (ii) an antibody which selectively binds to a molecule comprising the phosphorylated amino acid, said antibody being labeled with a donor fluorophore which corresponds to the acceptor fluorophore labeling said substrate; and (iii) a high-energy phosphate source; (b) measuring the FRET of the combination of step (a); and (c) using the FRET measurement of step (b) to determine the activity of the enzyme."

Thus, Epps et al. do not teach "providing a labelled first binding partner which binds to the protein in a manner dependent on the post-translational modification of the protein by the enzyme and which generates a signal in a manner dependent on said post-translational modification, and a second labelled binding partner which binds to said protein", as claimed in amended claim 2. Rather, Epps et al. teach contacting a substrate molecule with an enzyme and a single labeled antibody.

Eberwine et al. do not teach all of the elements of claim 2 and therefore do not anticipate claims 2-14 of the instant application.

In view of the above, Applicants respectfully request withdrawal of the rejection of claims 2-14 under 35 U.S.C. § 102(e) in view of Epps et al. (U.S. 6,203,994).

Rejection of claims 10-11 and 14 under 35 U.S.C. § 103(a)

Claims 10-11 and 14 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Prusiner et al. or Martinez et al. or Eberwine et al. in view of Epps et al. or Kinjo et al. (Nucleic Acids Research, 1995).

The Examiner states that "[i]t would have been obvious to one of ordinary skill in the art at the time of the instant invention to have substituted another known applicable detection assay such as FCS taught by Kinjo or FCS and FRET taught by Epps into the method of Prusiner, Martinez or Eberwine because Kinjo and Epps specifically taught that FCS and FRET are capable of functionally monitoring ligand interaction kinetics, conformational state and/or post-translational modification of proteins by enzyme".

Even if the references are combined, they do not provide the invention as claimed.

Applicant submits that even if Prusiner et al., Martinez et al. or Eberwine et al. are combined with Epps et al. or Kinjo et al., no combination of the disclosures would provide the invention as claimed in claims 10-11 and 14. That is, the recited combination lacks essential elements of the claimed invention.

Claims 10-11 and 14 depend from claims 1 and 2.

Claim 1 requires "contacting a protein with a labeled first binding partner which binds to said protein in a manner dependent on the conformational state of said protein and which

generates a signal in a manner dependent on the binding of the first binding partner to the protein, and a labeled second binding partner which binds to said protein, wherein said protein and said labeled first or second binding partner are not covalently coupled".

Applicant submits that none of Prusiner et al., Martinez et al., Eberwine et al., Epps et al. or Kinjo et al. teach or suggest contacting a protein with a labeled first binding partner which binds to the protein and a labeled second binding partner which binds to the protein.

Claim 2 requires "providing a labelled first binding partner which binds to the protein in a manner dependent on the post-translational modification of the protein by the enzyme and which generates a signal in a manner dependent on said post-translational modification, and a second labelled binding partner which binds to said protein".

Applicant submits that none of Prusiner et al., Martinez et al., Eberwine et al., Epps et al. or Kinjo et al. teach or suggest providing a labelled first binding partner which binds to the protein and a second binding partner which binds to the protein."

In view of the above, Applicants respectfully request withdrawal of the rejection of claims 10-11 and 14 under 35 U.S.C. § 103(a) over Prusiner et al. or Martinez et al. or Eberwine et al. in view of Epps et al. or Kinjo et al. (Nucleic Acids Research, 1995).

Rejection of claims 19-22 under 35 U.S.C. § 103(a)

Claims 19-22 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Prusiner et al. or Martinez et al. or Eberwine et al. or Epps et al. or Tsien et al. in view of Foster et al. U.S. 4,444, 879.

The Examiner states that "Foster et al. teaches kit components with instructions for use in assay methods. It would have been obvious to have incorporated the protein standards, binding partners and label reagents taught by Prusiner, Martinez, Tsien, Eberwine, and Epps into a kit format for use in a method of determining the conformational state of a protein because kit formats are recognized for their advantage in convenience and economy."

Even if the references are combined, they do not provide the invention as claimed.

Claims 19 requires "a labelled first binding partner which binds to the protein in a manner dependent on the conformational state of the protein and is detectable in a manner

dependent on its binding to the protein, and a labelled second binding partner, wherein said protein and said first binding partner are not covalently coupled".

Claim 20 and dependent claims 21-22 require "a labelled first binding partner which binds to the protein in a manner dependent on the conformational state of the protein and is detectable in a manner dependent on its binding to the protein and a labelled second binding partner, wherein said protein and said first binding partner or said second binding partner are not covalently coupled".

Prusiner et al., Martinez et al., Eberwine et al., Epps et al. and Tsien et al. have been discussed above.

Foster et al. teach methods and an apparatus for immunoassays. Foster et al. teach a kit for an enzyme immunoassay of the invention for the determination of immunoglobulins in test samples of body fluids.

Applicant submits that none of Prusiner et al., Martinez et al., Eberwine et al., Epps et al. Tsien et al. or Foster et al. teach or suggest "a labelled first binding partner which binds to the protein in a manner dependent on the conformational state of the protein and is detectable in a manner dependent on its binding to the protein, and a labelled second binding partner, wherein said protein and said first binding partner are not covalently coupled", as required by claim 19.

Applicant submits that none of Prusiner et al., Martinez et al., Eberwine et al., Epps et al. or Foster et al. teach or suggest "a labelled first binding partner which binds to the protein in a manner dependent on the conformational state of the protein and is detectable in a manner dependent on its binding to the protein and a labelled second binding partner, wherein said protein and said first binding partner or said second binding partner are not covalently coupled", as required by claims 20-22.

Applicant submits that even if Prusiner et al., Martinez et al. or Eberwine et al. or Epps et or Tsien et al. are combined with Foster et al, no combination of the disclosures would provide the invention as claimed in claims 19-22. That is, the recited combination lacks essential elements of the claimed invention.

In view of the above, Applicants respectfully request withdrawal of the rejection of claims 19-22 under 35 U.S.C. § 103(a) over Prusiner et al. or Martinez et al. or Eberwine et al. or Epps et al. or Tsien et al. in view of Foster et al.

Applicants submit that in view of the foregoing amendments and remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Craig and Colyer	Examiner:	Gabel
Serial No.:	09/511,776		
Filed:	2/24/00	Group Art Unit:	1641
Entitled:	Methods and Compositions Using Protein Binding Partners		

Commissioner for Patents
Washington, D.C. 20231

MARKED-UP CLAIMS

IN THE CLAIMS:

1. (Amended) A method for determining the conformational state of a protein, comprising the steps of:

a) contacting a protein with a labeled first binding partner which [is capable of binding] binds to [the] said protein in a manner dependent on the conformational state of [the] said protein and which generates a signal in a manner dependent on the binding of the first binding partner to the protein, and a labeled second binding partner which binds to said protein, wherein said protein and said labeled first or second binding partner are not covalently coupled; and

b) detecting [labelling of] said protein by the binding of at least one of [the] said labeled first binding partner or said labelled second binding partner to said protein wherein labelling of said protein is an indicator of the conformational state of said protein.

2. (Amended) A method for measuring the activity of an enzyme, wherein the conformation of a protein is dependent upon the post-translational modification activity of the enzyme, the method comprising the steps of:

a) contacting a protein comprising a site for post-translational modification with the enzyme;

b) providing a labelled first binding partner which [is capable of binding] binds to the protein in a manner dependent on the post-translational modification of the protein

by the enzyme and which generates a signal in a manner dependent on said post-translational modification, and a second labelled binding partner which binds to said protein;

c) contacting the protein with the labelled first binding partner and the labelled second binding partner and determining the post-translational modifying activity of the enzyme.

4. (Amended) The method of [any one of] claim[s] 1 or 2 [to 3], wherein the protein is immobilised on a solid phase substrate.

5. (Amended) The method of claim 1 or 2 [3], wherein the second binding partner is a capture ligand, and said protein that binds to said capture ligand [the protein] is isolated [by binding] from said protein that does not bind to said capture ligand.

6. (Amended) The method of claim 5, wherein said capture ligand is bound to a solid phase [support] substrate.

7. (Amended) The method of claim 1 or claim 2, wherein at least one of said first [and/] or second binding partner is labeled with a label selected from the group consisting of a fluorescent label, [or other] a chemiluminescent label, a domain of an enzyme, a radiolabel, a chemical or enzymatic label and a heavy metal [or other radioopaque] label.

10. (Amended) The method of claim [9] 1 or 2, wherein both said first and second binding partners are fluorescently labelled, [the labels are fluorescent] and the binding of said binding partners to the protein is assayed by fluorescence resonance energy transfer (FRET).

11. (Amended) The method of claim 8, wherein both said first and second binding partners are labelled, with [the labels are] enzyme domains, which associate to form a functional receptor molecule when both binding partners are bound to the protein.

13. (Amended) The method of [any one of claims 4 to 6 or 12] claim 1 or 2, wherein unbound labelled first binding partner is removed to allow detection of the binding of the labelled first binding partner to the protein.

14. (Amended) The method of claim 8, wherein the labelling of the protein by the binding of said first binding partner is detected by fluorescence correlation spectroscopy (FCS).

19. (Amended) A kit for the determination of the conformational state of a protein in a sample, comprising:

a) a labelled first binding partner which binds to the protein in a manner dependent on the conformational state of the protein and is detectable in a manner dependent on its binding to the protein and a labelled second binding partner, wherein said protein and said first binding partner or said second binding partner are not covalently coupled [according to claim 15]; and

b) packaging components.

20. (Amended) A kit for the determination of the presence of a ligand for a protein in a sample, comprising:

a) a protein which binds to the ligand the presence of which is to be determined and which undergoes a conformational change as a result of such binding;

b) a labelled first binding partner [according to claim 15] which binds to the protein in a manner dependent on the conformational state of the protein and is detectable in a manner dependent on its binding to the protein [conformationally-dependent manner] and a labelled second binding partner, wherein said protein and said first binding partner or said second binding partner are not covalently coupled; and

c) packaging components.

22. (Amended) The kit of clam 21, wherein at least one of the first [and/] or second binding partner is labelled.